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EXAMINER

WOITACH, JOSEPH T

ART UNIT

PAPER NUMBER

1632

DATE MAILED: 07/31/2002

20

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|-----------------|-----------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 09/473,872 | YOON, KYONGGEUN |
| | Examiner | Art Unit |
| | Joseph Woitach | 1632 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 07 May 2002.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-40 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1-40 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. _____.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

| | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This application is an original application filed December 28, 1999.

Applicant's amendment filed May 7, 2002, paper number 19, has been received and entered. Claims 1 and 32 have been amended. Claims 1-40 are pending and currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claim 1 is vague and unclear. First, it is noted that the claim amendments have obviated the specific basis of the previous rejection. However, in the amendment deleting the recitation of 'a composition [sufficient to bring about stable genetic and phenotypic modifications in the selected gene]', the RNA-DNA oligonucleotide no longer has any functional limitation which clearly defines the activity. It is noted that the RNA-DNA oligonucleotide has structural limitations, however it is unclear whether any oligonucleotide having a double hairpin structure

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with pyrimidine loops would result in modifying a selected gene, or if the RNA-DNA has the structural limitations necessary and/or sufficient to cause a genetic alteration. There is not nexus between the RNA-DNA oligonucleotide in the composition and its ability to modify any gene. Amending the claim to more clearly reflect the critical properties of the RNA-DNA oligonucleotide which affect the stable genetic change would obviate the basis of the rejection. Dependent claims 2-17 are included in this rejection because they fail to clarify the basis of the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 32-34 and 37-39 stand rejected under 35 U.S.C. 102(b) as being anticipated by Alexeev *et al.* (IDS reference).

Applicant points out that Alexeev *et al.* teach methods for modifying cells *in vitro*, and do not teach an animal generated by the instantly claimed method. Applicant argues that Alexeev *et al.* does not teach an animal model having a skin disorder which would anticipate the instant

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claims. See Applicant's amendment, paragraph bridging pages 2-3. Applicant's arguments have been fully considered but not found persuasive.

The amendment to the claim to encompass a non-human animal model is noted. However, as noted in the previous office action, claim 32 broadly encompasses an animal model having a skin disorder wherein the disorder comprises a mutation generated in a gene which leads to said disorder, and dependent claims 33-39 are drawn to specific genes and specific types of mutations. Examiner notes that Alexeev *et al.* teach methods to correct a particular gene mutation in cells *in vitro*, however the cells for the study are isolated from an animal whose skin cells display the phenotype of albino melanocyte. The basis of anticipation is the albino mouse which contains the specific point mutation which results in the albino phenotype. Therefore, the animals taught by Alexeev *et al.* represent an animal model for the study of a mutation in the Tyr gene, and thus, anticipate the claims. Case law states that where the claimed and prior art products are identical or substantially identical in structure or composition, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Examiner conceded that the animal disclosed by Alexeev *et al.* are not made by the instantly claimed process, however the resulting animal containing a mutation which results in an albino phenotype would be indistinguishable from that disclosed in Alexeev *et al.* Case law states that a

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prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985), *In re Ludtke*, 441 F.2d 660, 169 USPQ 563 (CCPA 1971), *Northam Warren Corp. v. D. F. Newfield Co.*, 7 F. Supp. 773, 22 USPQ 313 (E.D.N.Y. 1934) and MPEP 2112.01. In the instant case, the instantly claimed animal model is presented as a product by process claim, however there is no evidence of record, nor has Applicant provided evidence that the albino mouse disclosed in Alexeev *et al.*, or any other animal containing a mutation which results in an observable phenotype, would be any different if it were generated by altering the genome of a normal mouse by using the instantly claimed method.

Thus, the animals containing a mutation in the Tyr gene as taught by Alexeev *et al.* represent an animal model which anticipates the instant claims. Therefore, for the reasons above and of record, the rejection is maintained.

Claims 32-33, 35 and 37-39 rejected under 35 U.S.C. 102(b) as being anticipated by Christiano *et al.* (PNAS, 91:3549-3553, 1994) is withdrawn.

The amendment of the claim to recite a non-human animal model has differentiated the instantly claimed product from that disclosed by Christiano *et al.* who teach a pedigree of Finnish individuals whose genome contains a mutation in the COL7A1 gene.

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Claims 32-33 and 36-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Uttam *et al.* (PNAS 93:9079-9084, 1996) is withdrawn.

The amendment of the claim to recite a non-human animal model has differentiated the instantly claimed product from that disclosed by Uttam *et al.* who teach a pedigree of German individuals whose genome contains a mutation in the keratin 14 gene.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-40 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Yoon *et al.* (PNAS, 1996) and Alexeev *et al.* (Nature Biotech, 1998) in further view of, Uttam *et al.* (PNAS, 1996), Christiano *et al.* (PNAS, 1994) and Cole-Strauss *et al.* (IDS reference; Science, 1996).

Applicant summarizes the teaching of Yoon *et al.* noting that the experiments performed were done with cells *in vitro*, and note that none of the remaining references provide the guidance, motivation or expectation of success to practice the methods *in vivo* citing *Micro Chemical, Inc. v Great Plains Chemical Co., Inc.*, in support of their argument. Additionally, Applicant reviews the teachings of Alexeev *et al.* and argue that based on the efficiency observed by Alexeev *et al.* one of skill in the art would not have expected the high frequency observed and

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disclosed in the present specification, citing *In re Dow Chemical Co.* and *In re Soni* in support of their arguments. See Applicant's amendment, pages 3-6. Applicant's arguments have been fully considered but not found persuasive.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 19880; *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In the instant case, Yoon *et al.* in summary of their results specifically state that their observations 'should extent the applicability of this therapeutic strategy to human genetic diseases' (bottom of first column, page 2076) and clearly provide the basis for the use of the specific methodology for affecting gene therapy to correct disease related mutations (page 2071, introductory comments). Cole-Strauss *et al.* provide similar motivation indicating that the instantly claimed methods hold promise as a therapeutic method for treatment of genetic diseases. Alexeev *et al.* provide evidence that the methodology is effective in correcting albinism a phenotype of a skin related to single point mutation. Uttam *et al.* and Christiano *et al.* are relied upon solely to demonstrate that other skin disorders/diseases and the particular mutations which give rise to said disorders/diseases are known and described in detail. Clearly the general methodology described in the present specification was known at the time of filing, and clearly its use was

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proposed for gene therapy protocols to correct known mutations associated with particular diseases, including the skin disorder albinism. Finally, it is noted that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988). In the instant case, there is no teaching that would lead one to believe that the instantly claimed methods would not work, and to the contrary, the references indicate that the methods were being developed for use in affecting gene therapy protocols.

With regard to the unexpected results Applicant's argue are disclosed in the present specification, it is noted that the instantly claimed methods are not specifically drawn to the unexpected result pointed to by Applicant. Yoon *et al.*, Cole-Strauss *et al.* and Alexeev *et al.* clearly demonstrate that the methodology can be used to successfully alter the genome of a cell. Further, it is noted that Yoon *et al.* indicate that different RNA-DNA oligonucleotide constructs provide a varying degree of efficiency ranging from low levels to a frequency of 30% (top of first column, page 2074). In review of *In re Soni*, 34 USPQ2d 1684 (CA FC 1995) it is found that consistent with the rule that all evidence of nonobviousness must be considered when assessing patentability, the PTO must consider comparative data in the specification in determining whether the claimed invention provides unexpected results. *In re Margolis*, 785 F.2d 1029, 1031, 228 USPQ 940, 941-42 (Fed. Cir. 1986). However, " [i]t is well settled that unexpected results must be established by factual evidence. Mere argument or conclusory statements in the specification does not suffice." *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed.

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Cir. 1984); see also *In re Wood*, 582 F.2d 638, 642, 199 USPQ 137, 140 (CCPA 1978) ("Mere lawyer's arguments and conclusory statements in the specification, unsupported by objective evidence, are insufficient to establish unexpected results."); *In re Lindner*, 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972) ("[M]ere conclusory statements in the specification . . . are entitled to little weight when the Patent Office questions the efficacy of those statements."). In the instant case, the question is not whether the claimed methods would work, rather would each and every embodiment provide an unexpected result commensurate in scope with that pointed to by Applicant. Clearly, Yoon *et al.* demonstrate that there is variation in the effectiveness of one construct to another for one gene, and the results of Cole-Strauss *et al.* and Alexeev *et al.* demonstrate that varying results can be expected for other different genes. As discussed in *In re Soni* the unexpected results must be commensurate in scope with the claims. See *In re Dill*, 604 F.2d 1356, 1361, 202 USPQ 805, 808 (CCPA 1979) ("The evidence presented to rebut a *prima facie* case of obviousness must be commensurate in scope with the claims to which it pertains."). Here, the instantly claimed method does not recite the specific parameters used to obtain the result indicated as unexpected, and the evidence of record does not indicate that the unexpected result would necessarily extend to any construct and to any gene.

Thus, for the reasons above and of record, the claimed invention, as a whole was *prima facie* obvious absent to the evidence to the contrary. Therefore, the rejection is maintained.

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Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist Pauline Farrier whose telephone number is (703)305-3550.

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Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

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